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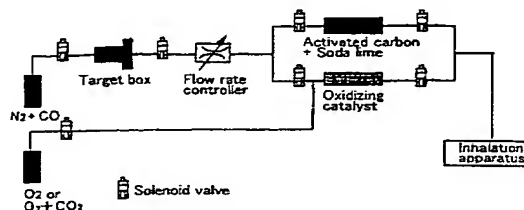MIYAKE, YOSHINORI (JP).
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(54) PROCEDES DE PRODUCTION DE MONOXYDE DE <SP>15</SP>O-CARBONE ET DE DIOXYDE DE <SP>15</SP>O-CARBONE ET APPAREIL DE PRODUCTION

(54) PROCESSES FOR PRODUCING 15O-CARBON MONOXIDE AND 15O-CARBON DIOXIDE AND PRODUCTION APPARATUS

(57) Nitrogen gas containing carbon monoxide is irradiated with deuteron beams, and the [15O]CO generated by a nuclear reaction is recovered. Since no heating step is necessary, [15O]CO can be easily supplied in a short time. Also provided is a method of generating [15O]CO2 which comprises bringing [15O]CO into contact with an oxidation catalyst. The use of an oxidation catalyst enables [15O]CO2 to be generated at ordinary temperature.

(54) Titre : PROCEDES DE PRODUCTION DE MONOXYDE DE ^{15}O-CARBONE ET DE DIOXYDE DE ^{15}O-CARBONE ET APPAREIL DE PRODUCTION
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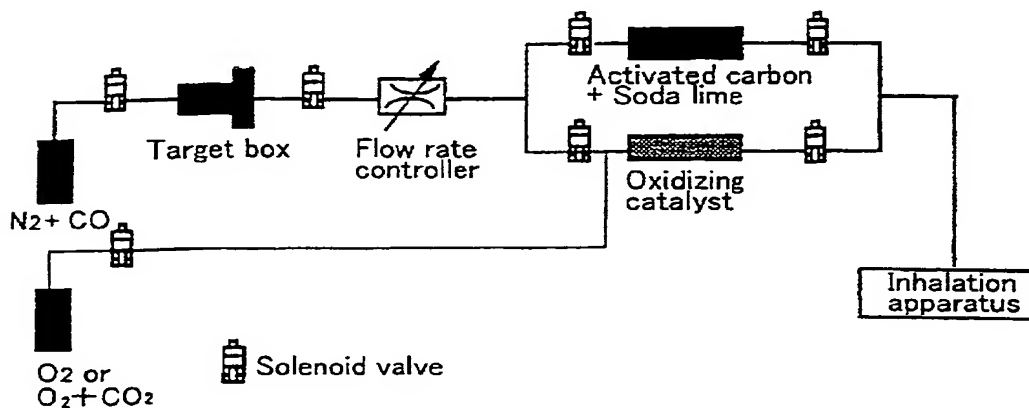
(57) Abrégé/Abstract:
Nitrogen gas containing carbon monoxide is irradiated with deuteron beams, and the [^{15}O]CO generated by a nuclear reaction is recovered. Since no heating step is necessary, [^{15}O]CO can be easily supplied in a short time. Also provided is a method of generating [^{15}O]CO$_2$ which comprises bringing [^{15}O]CO into contact with an oxidation catalyst. The use of an oxidation catalyst enables [^{15}O]CO$_2$ to be generated at ordinary temperature.

ABSTRACT

As the gas to be irradiated, a nitrogen gas comprising carbon monoxide is irradiated with a deuteron beam, and $[^{15}O]CO$

5   produced by nuclear reaction is recovered. Since a heating process is not required, $[^{15}O]CO$ can be easily supplied in a short time.

Furthermore, the present invention provides a method for producing $[^{15}O]CO_2$ by contacting $[^{15}O]CO$ with oxidizing catalysts.

10   $[^{15}O]CO_2$ can be produced at room temperature by using oxidizing catalysts.
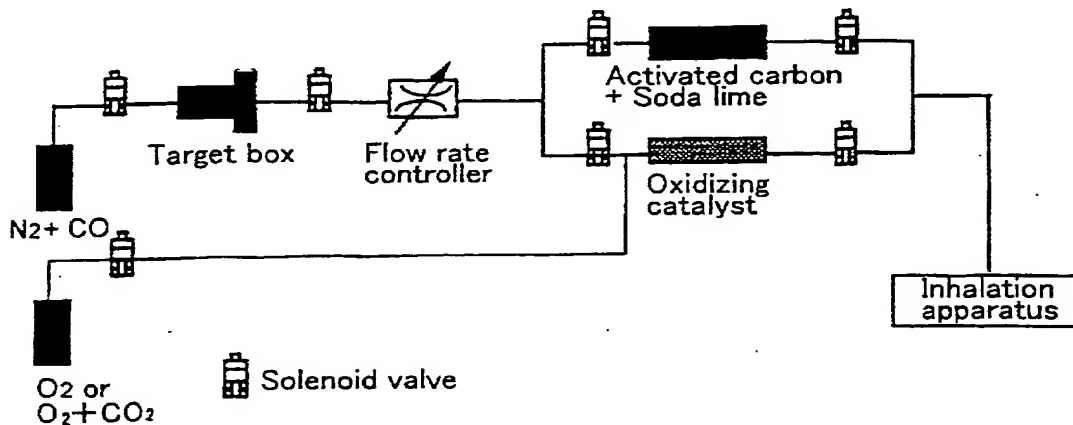
DESCRIPTION

METHODS AND APPARATUS FOR PRODUCING ^{15}O-CARBON MONOXIDE AND ^{15}O-CARBON DIOXIDE

Technical Field

The present invention relates to ^{15}O-carbon monoxide and ^{15}O-carbon dioxide, which are useful in positron emission tomography (PET). ^{15}O-carbon monoxide and ^{15}O-carbon dioxide are used to measure the level of oxygen metabolism, important information for identifying ischemic conditions in brain tissue.

Hereinafter, ^{15}O-carbon monoxide is represented by $C^{15}O$, and ^{15}O-carbon dioxide is represented by $C^{15}O_2$. Furthermore, carbon monoxide comprising $C^{15}O$ is represented by $[^{15}O]CO$, and carbon dioxide comprising $C^{15}O_2$ is represented by $[^{15}O]CO_2$.

Background Art

Positrons (positive electrons) are antiparticles comprising a charge opposite to that of electrons. On colliding with electrons, positrons discharge γ-rays and then disappear (β^+ decay). Elements comprising positrons in their nucleus are called positron nuclides. Positron nuclides can be obtained by irradiating light elements with proton or deuteron beams to produce elements in which the number of protons is larger than the number of neutrons. ^{11}C, ^{13}N, ^{15}O, ^{18}F, and such are known as positron nuclides. For example, while the number of neutrons in normal element ^{16}O is eight, the number of neutrons in positron nuclide ^{15}O is seven, less than the number of its protons, which is eight. Therefore, ^{15}O discharges a positron to reduce its protons to seven, resulting in a stable nitrogen element.

The half-life of positron nuclides is very short: about 20 minutes for ^{11}C, and 118-130 seconds for ^{15}O. Since positron nuclide radioactivity decreases rapidly, synthesis of tracer labels and kinetics measurement and such are time-constrained. However, since positron nuclides comprise the following advantages, they are applied in the field of nuclear medicine

in diagnosing living organisms. The diagnostic method utilizing positron nuclides is called positron emission tomography (PET).

(1) These positron nuclides are isotopes of elements that make up molecules originally present in living organisms. Therefore, by utilizing positron nuclides as tracers, the metabolic condition of living organisms can be observed without modifying molecules present in organisms.

(2) Due to their short half-life, exposure to living organisms is low (repeated tests and challenge tests can be carried out).

(3) Due to their short half-life, specific radioactivity is high, and thus diagnosis using trace amounts of nuclide is possible.

In PET, the location of a tracer in a three-dimensional space in a living organism is converted into an image, based on the theory below. As described above, positrons collide with electrons and discharge γ-rays. Specifically, two annihilation photons (γ-rays) with an energy of 511 keV are emitted in opposite directions, at 180° to each other. The emitted γ-rays are measured using radiation detectors placed in a straight line. When counted by a coincidence circuit, nuclear decay is found to occur along this straight line. Furthermore, when these detectors are placed in a 360° circle, the distribution of positron nuclides can be tomographically imaged based on approximately the same theory as X-ray CT. Additionally, the amount of detected radiation can be quantitatively determined.

In PET, the concentration of positron nuclides inside the body is accumulated as tomographic images. Consequently, if a region of interest (ROI) is set in an arbitrary portion, the concentration of positron nuclides at this position can also be determined. Furthermore, when a tracer's metabolic pathway is already known, and a kinetics analysis model in the body has been established, the tracer's behavior in the body can be quantitatively understood. By utilizing such PET features, the metabolic condition of various organs can be non-invasively

observed, from outside of the body. As the diagnostic methods using PET, for example, the following diagnoses are in practical use:

Tracer	Diagnostic target
^{15}O gas	Local cerebral oxygen metabolism
$[^{15}O]CO$ gas	Local cerebral blood volume
$[^{15}O]CO_2$ gas	Local cerebral blood flow
$^{15}O-H_2O$	Local cerebral blood flow
$^{18}F-DG$	Glucose metabolism
$^{18}F-DOPA$	Dopamine-based neural transmission function

5

For example, in cerebral stroke therapy, appropriate treatment within three hours of onset is said to significantly influence the subsequent medical condition. Thus, rapid and accurate understanding of post-onset cerebral oxygen metabolism

10 is important for treatment. At present, PET examinations are the only examinations capable of correctly understanding cerebral oxygen metabolism.

PET examination of cerebral oxygen metabolism is conducted as described below. First, a test subject inhales the

15 following three gases as tracers:
$[^{15}O]CO$ gas; $[^{15}O]CO_2$ gas; and ^{15}O gas.

After inhalation, tracer distribution in the subject's head is traced using PET. Local cerebral blood volume, local cerebral blood flow, and local cerebral oxygen uptake ratio can

20 be measured. Based on the results of these measurements, the degree of local cerebral oxygen metabolism is calculated.

Inhalation of the three above-mentioned ^{15}O-labeled gases is necessary for PET examination of cerebral oxygen metabolism. Due to the preparation of each gas and photography, examination

25 takes about two hours. The applicable scope of this examination is significantly limited, since examination of patients seeking treatment within three hours of onset requires two or more hours. In fact, the value of examination results is increased by initiating examination as soon as possible

after onset. Therefore, technology that enables examination of cerebral oxygen metabolism in a shorter time is required.

Enhanced acute-stage medical care for cerebral stroke is necessary in an aging society. Test methods able to be performed within 30 minutes have been developed as test methods for cerebral stroke, which requires rapid examination. For example, in about five to 30 minutes, diagnostic imaging of the brain by X-ray computed tomography (CT) and magnetic resonance imaging (MRI) can be performed. These examinations are effective for diagnosing cerebrovascular disorders such as hemorrhage and infarction. However, when using X-ray CT and MRI it is difficult to understand the brain tissue dysfunctions caused by to these cerebrovascular disorders. To confirm the condition of brain tissue, examination of local cerebral oxygen metabolism is necessary. Therefore, even after the practical application of these examination methods, which can be performed in a short time, examination of cerebral oxygen metabolism using ^{15}O as a tracer is important.

In general, a ^{15}O gas is prepared by the following process. First, nitrogen gas comprising 0.5% to 2.5% oxygen gas is irradiated with deuterons. ^{15}O gas is then generated by the nuclear reaction of $^{14}N(d,n)^{15}O$. Deuterons are irradiated using a cyclotron. ^{15}O gas thus-produced is itself utilized as an inhalation gas for examining cerebral oxygen metabolism using the above-mentioned PET. In addition, it can also be utilized in the preparation of $[^{15}O]CO$ gases. A $[^{15}O]CO$ gas can be prepared by reacting the recovered ^{15}O gas with activated carbon heated to 1000°C.

$[^{15}O]CO_2$ gas required for PET examination of cerebral oxygen metabolism is also prepared as described below. First, nitrogen gas comprising 0.25% to 2.5% oxygen gas is irradiated with deuterons. ^{15}O gas is then generated by the nuclear reaction of $^{14}N(d,n)^{15}O$. A $[^{15}O]CO_2$ gas can be prepared by reacting the recovered ^{15}O gas with activated carbon heated to 400°C.

In addition, a method is also known for directly

synthesizing a $[^{15}O]CO_2$ gas, and the target gas in this method is nitrogen gas comprising carbon dioxide (Mackay DB, Quality assurance for PET gas production using the Cyclone 3D oxygen-15 generator. Applied Radiation and Isotopes, 51, 1999, 403-409).

5   In this method, carbon dioxide synthesis does not require a heating process. However, an activated carbon column heated to 500°C is required when removing carbon monoxide generated by deuteron beam irradiation. Thus, this method also necessitates a heating process.

10   As described above, known methods for preparing $[^{15}O]CO$ and $[^{15}O]CO_2$ require a step of contacting the gas with activated carbon, a catalyst, or an adsorbent under conditions of high temperature. In general, high temperature conditions are created by heating an electric furnace. However, heating an

15   electric furnace requires considerable time, precluding any reduction in the duration of the tracer gas supply process. If $[^{15}O]CO$ and $[^{15}O]CO_2$ can be produced at lower temperatures, tracer gases can be produced in a shorter period of time. If tracer gases can be supplied in a shorter period of time, PET

20   examination of cerebral oxygen metabolism can be completed in a shorter time. By early diagnosis, more efficient methods of cerebral stroke treatment can be selected. Furthermore, by reducing examination time, necessary examinations can be performed on a larger number of patients.

25

Disclosure of the Invention

An objective of the present invention is to provide methods for preparing $[^{15}O]CO$ and $[^{15}O]CO_2$ in a short period of time. More specifically, an objective of the present invention

30   is to provide methods for preparing $[^{15}O]CO$ and $[^{15}O]CO_2$ that do not require conditions of high temperature.

As a result of various investigations to achieve this objective, the present inventions discovered that $[^{15}O]CO$ is continuously generated immediately after a target gas is

35   irradiated with deuterons. Furthermore, the present inventors also discovered that $[^{15}O]CO$ can be rapidly converted into ^{15}O-

carbon dioxide at room temperature by using an oxidizing agent. The present inventors have found that the length of a PET examination of cerebral oxygen metabolism can be significantly reduced by utilizing the $[^{15}O]CO$ and $[^{15}O]CO_2$ obtained by these methods, thus completing the present invention.

Namely, the present invention relates to methods for producing $[^{15}O]CO$ or $[^{15}O]CO_2$, and apparatuses for the same.

[1] A method for producing ^{15}O-carbon monoxide, which comprises the steps of:

(1) using a nitrogen gas comprising carbon monoxide as a gas to be irradiated, and irradiating the gas with a deuteron beam; and

(2) recovering ^{15}O-carbon monoxide produced by the deuteron beam irradiation.

[2] The method according to [1], wherein the amount of carbon monoxide comprised in the gas to be irradiated is 0.01 to 0.5 v/v%.

[3] The method according to [2], wherein the amount of carbon monoxide comprised in the gas to be irradiated is 0.05 to 0.2 v/v%.

[4] The method according to [1], which comprises the step of contacting the irradiated gas with a nitrogen oxide adsorbent and/or a carbon dioxide adsorbent, and recovering ^{15}O-carbon monoxide.

[5] The method according to [1], wherein the gas to be irradiated is continuously supplied while recovering the produced ^{15}O-carbon monoxide.

[6] An apparatus for producing ^{15}O-carbon monoxide, which comprises:

(1) a target box through which a gas to be irradiated can be passed and in which the gas to be irradiated can be irradiated with a deuteron beam;

(2) a means of supplying the gas to be irradiated, which supplies the target box of (1) with a nitrogen gas comprising carbon monoxide as the gas to be irradiated; and

(3) a means for recovering ^{15}O-carbon monoxide.

[7] The apparatus according to [6], wherein the means of (3) for recovering ^{15}O-carbon monoxide comprises:

a means for receiving the gas to be irradiated in the target box of (1); and

a nitrogen oxide adsorbent and/or a carbon dioxide adsorbent.

[8] The apparatus according to [6], wherein the means for supplying the gas to be irradiated of (2) can continuously supply the target box of (1) with the gas to be irradiated.

[9] The apparatus according to [6], wherein the means of (3) for recovering ^{15}O-carbon monoxide is connected to a line for supplying ^{15}O-carbon monoxide to a subject.

[10] A method for producing ^{15}O-carbon dioxide, which comprises the steps of:

(1) contacting ^{15}O-carbon monoxide with an oxidizing catalyst in the presence of dry oxygen; and

(2) recovering the produced ^{15}O-carbon dioxide.

[11] The method according to [10], wherein the dry oxygen is a mixed gas comprising dry carbon dioxide.

[12] The method according to [10] for producing ^{15}O-carbon monoxide, which comprises the steps of:

i) supplying the target box with a nitrogen gas comprising carbon monoxide as the gas to be irradiated; and

ii) irradiating the gas to be irradiated with a deuteron beam to produce ^{15}O-carbon monoxide.

[13] An apparatus for producing ^{15}O-carbon dioxide, which comprises:

(1) a means for supplying ^{15}O-carbon monoxide;

(2) an oxidizing catalyst for oxidizing carbon monoxide;

(3) a means for supplying dry oxygen to the oxidizing catalyst; and

(4) a means for recovering ^{15}O-carbon dioxide.

[14] The apparatus according to [13], wherein the means of (1) for supplying ^{15}O-carbon monoxide is a ^{15}O-carbon monoxide-producing apparatus that comprises:

i) a target box through which a gas to be irradiated can be passed, and in which the gas to be irradiated can be irradiated with a deuteron beam; and

ii) a means for supplying the gas to be irradiated which
5   supplies the target box of (i) with a nitrogen gas comprising carbon monoxide as the gas to be irradiated.

[15] A method for producing ^{15}O-carbon monoxide and ^{15}O-carbon dioxide, which comprises the steps of:

(1) using a nitrogen gas comprising carbon monoxide as a
10 gas to be irradiated, and irradiating the gas with a deuteron beam;

(2) recovering the ^{15}O-carbon monoxide produced by the deuteron beam irradiation;

(3) contacting the irradiated gas with an oxidizing
15 catalyst in the presence of dry oxygen; and

(4) recovering ^{15}O-carbon dioxide produced in the step of (3).

[16] An apparatus for producing ^{15}O-carbon monoxide and ^{15}O-carbon dioxide, which comprises:

20 (1) a target box through which a gas to be irradiated can be passed, and in which the gas to be irradiated can be irradiated with a deuteron beam;

(2) a means for supplying the gas to be irradiated, which supplies the target box with a nitrogen gas comprising carbon
25 monoxide as the gas to be irradiated;

(3) a means for recovering ^{15}O-carbon monoxide;

(4) an oxidizing catalyst for oxidizing carbon monoxide;

(5) a means for supplying dry oxygen to the oxidizing catalyst; and

30 (6) a means for recovering ^{15}O-carbon dioxide.

Furthermore, the present invention provides methods for examining cerebral blood flow, which comprise the steps of:

(1) administering a subject with [^{15}O]CO produced by the
35 method of [1], [^{15}O]CO$_2$ produced by the method of [10], and ^{15}O;

(2) detecting the distribution of positron nuclide ^{15}O in

the subject's brain; and

(3) based on the distribution of positron nuclide ^{15}O, determining at least one parameter selected from the group consisting of local cerebral blood volume, local cerebral blood flow, and local cerebral oxygen uptake ratio.

Furthermore, the present invention provides methods for examining the degree of local cerebral oxygen metabolism, based on the above-mentioned examination methods. Namely, the present invention relates to methods for examining the degree of local cerebral oxygen metabolism, which comprise the steps of:

(1) using an above-mentioned cerebral blood flow examination method to determine local cerebral blood volume, local cerebral blood flow, and local cerebral oxygen uptake ratio; and

(2) determining the degree of local cerebral oxygen metabolism based on the parameters determined in (1).

The present invention relates to methods for producing $[^{15}O]CO$, which comprise the steps of:

(1) using a nitrogen gas comprising carbon monoxide as the gas to be irradiated, and irradiating the gas to be irradiated with a deuteron beam;

(2) recovering $[^{15}O]CO$ produced by the deuteron beam irradiation.

In the present invention, a "gas to be irradiated" means a gas to which a carrier gas is added. In general, "target gas" means a gas comprising, in a gaseous state, elements that produce positron nuclides by nuclear reaction. In the present invention, the target gas can be high purity nitrogen gas which comprises a small amount of carbon monoxide as a carrier. A high purity gas is used as the target gas (nitrogen gas). ^{14}N is generally used as the nitrogen gas. ^{15}N can also be used to obtain positron nuclides by $^{15}N(p,n)^{15}O$ reaction, but is expensive. Therefore, a preferable target gas is high purity nitrogen gas (^{14}N). In the present invention, "high purity gas" denotes a gas of 99.9999 purity or more.

The gas to be irradiated of the present invention comprises carbon monoxide gas as a carrier. Carbon monoxide gas is added for the recovery of $[^{15}O]CO$ in the gas irradiated with deuteron beams. The percentage of carbon monoxide gas in the gas to be irradiated is usually 0.5% or less. For example, depending on the concentration of carbon monoxide gas, when $[^{15}O]CO_2$ is synthesized using oxidizing catalysts as described below, non-radioactive by-products may be produced since oxidizing catalysts increase temperature. Therefore, it is usually preferable that the concentration of carbon monoxide gas is 0.5% or less. Furthermore, the $[^{15}O]CO$ inhaled by a subject should be of a concentration that does not risk carbon monoxide poisoning. In general, a safe range for carbon monoxide poisoning is said to be less than 1%. Consequently, 0.5% or less carbon monoxide gas is also preferable from the standpoint of safety. More specifically, 0.05 to 0.1% v/v of carbon monoxide gas is preferable.

In the present invention, the gas to be irradiated is irradiated with deuteron beams. In general, the gas to be irradiated is irradiated by passing deuteron beams through a part of its flow pass. Preferably, the part of the flow pass of the gas to be irradiated through which deuteron beams pass comprises a structure able to store a certain amount of the gas to be irradiated. In the present invention, the structure capable of storing the gas to be irradiated is called a "target box". The target box constitutes a part of the flow pass of the gas to be irradiated, and can be a space with a large volume that partially constitutes the flow pass. Furthermore, to store the gas to be irradiated, the target box can also comprise a mechanism for controlling the flow of the gas to be irradiated. The target box has some length in the traveling direction of the deuteron beams, allowing effective irradiation of the gas to be irradiated. The material of the target box is not particularly limited, as long as it allows permeation of deuteron beams and hermetically seals the gas to be irradiated. In general, an aluminum-magnesium alloy is used as the target

box material.

When the gas to be irradiated is irradiated with deuteron beams under suitable conditions, $[^{15}O]CO$ is continuously generated from a target gas, nitrogen, immediately after

5   irradiation. In this case, $[^{15}O]CO$ is considered to be generated by the recoil energy of $^{14}N(d,n)^{15}O$ reaction products. For example, when the above-mentioned target gas is irradiated with 6-10 MeV deuterons, $[^{15}O]CO$ can be produced continuously, immediately after deuteron irradiation.

10   $[^{15}O]CO$ generated by deuteron beam irradiation can be made to flow out of the target box by continually supplying new gas to be irradiated to the target box. $C^{15}O$ produced by a method of the present invention can be obtained as a gas mixture with a carrier gas by recovering radiated gas from the gas that has

15   flowed out. Furthermore, impurities can also be removed as necessary. When a nitrogen gas comprising carbon monoxide is used as the gas to be irradiated, the gas may comprise carbon dioxide generated by carbon monoxide oxidation, nitrogen oxide generated by nitrogen oxidation, and the like. Since these by-

20   products may impart an erroneous result in PET examination of cerebral oxygen metabolism, they are preferably removed in advance.

Methods for removing these by-products are well known. For example, carbon dioxide can be absorbed and removed by

25   passing through a soda lime column. Nitrogen oxide can be effectively removed by passing through an activated carbon column. The gas to be irradiated from which by-products have been removed can be used as an inhalation gas for PET examination of cerebral oxygen metabolism, after adjusting

30   carbon monoxide concentration, and mixing with other gases, as necessary. The inhalation gas is generally prepared by mixing a large amount of air (20 to 40 L/min) with a gas to be irradiated (300 to 500 mL/min) that comprises $[^{15}O]$ gas.

The $[^{15}O]CO$ production methods of the present invention,

35   which lead from supplying the gas to be irradiated to removing by-products, can be performed using well-known positron

synthesis apparatus. The present invention relates to [^{15}O]CO production apparatus comprising:

(a) a target box through which a gas to be irradiated can pass, and in which that gas is irradiated by deuteron beams;

5 (b) a means for supplying the gas to be irradiated, which supplies the target box of (a) with a nitrogen gas comprising carbon monoxide as the gas to be irradiated; and

(c) a means for recovering [^{15}O]CO.

The target box of (a) is connected to the means for 10 supplying the gas to be irradiated of (b). The means of (b) supplies the target box of (a) with the above-mentioned target gas comprising a suitable concentration of carbon monoxide. To regulate carbon monoxide concentration and control the amount of the gas to be irradiated supplied to the target box (a), the 15 means for supplying the gas to be irradiated of (b) can comprise a gas flow rate regulation mechanism. The gas flow rate regulation mechanism is made up of, for example, a solenoid valve and a gas flow meter. The carbon monoxide concentration and amount of target gas supplied are regulated 20 by regulating the flow rate of a target gas and carbon monoxide. They can also be managed to maintain a given numerical value by using a computer system that monitors gas flow rate.

The gas to be irradiated that is supplied to the target box of (a) is irradiated with deuteron beams. The target box 25 is made of a material for which irradiation by deuteron beams is possible, and placed at a deuteron beam irradiation position. To efficiently irradiate the gas to be irradiated with deuteron beams, the target box preferably comprises a form capable of aligning the gas to be irradiated in the direction in which the 30 deuteron beams are traveling.

Deuteron beams can be supplied by a cyclotron. Cyclotrons that radiate deuteron beams are well known. A typical cyclotron is made up of an ion source, accelerating electrodes, and the like. Since deuterons comprising an energy of 4-8 MeV 35 cause ^{14}N(d,n)^{15}O nuclear reactions to generate ^{15}O compounds, a cyclotron accelerator with an acceleration capability in this

energy range is suitable for medical applications. The charged
particles used in the nuclear reactions are all positive,
however, there are positive charge acceleration-types and
negative charge-types, depending on differences in the charge
5 of the particles while accelerating.

The means of (c) for recovering $[^{15}O]CO$ is a means for
recovering a gas to be irradiated which has been irradiated
with deuterons in the target box of (a). The means of (c) for
recovering $[^{15}O]CO$ can be, for example, a gas flow pass
10 connected to the target box of (a). The means of (c) for
recovering $[^{15}O]CO$ can comprise a flow rate controller capable
of controlling the flow rate of a gas to be irradiated that
flows from the target box of (a). The flow rate controller
monitors the flow rate of the gas to be irradiated that is
15 flowing in a flow pass, and controls solenoid valves provided
at respective positions according to the production processes,
to totally control the amount of the gas to be irradiated
flowing in the apparatus of the present invention. For example,
when irradiating with deuterons, the amount of the gas to be
20 irradiated that passes through the target box of (a) is
controlled so as to store the gas to be irradiated in the
target box of (a), in order to irradiate the necessary dose.
When recovering the irradiated gas, new gas to be irradiated is
fed into the target box of (a), and the irradiated gas flows
25 out of the target box of (a) and is recovered downstream of the
target box of (a). The gas to be irradiated can be
continuously supplied, and deuteron beam irradiation and
recovery of the irradiated gas can also be carried out
continuously.

30 In the $[^{15}O]CO$ production apparatus of the present
invention, the means of (c) for recovering $[^{15}O]CO$ can comprise
a means for removing by-products comprised in the gas to be
irradiated. Specifically, for example, carbon dioxide can be
absorbed and removed by passing through a soda lime column.
35 Nitrogen oxide can be removed effectively by passing through an
activated carbon column. Since these by-products can be

removed at normal temperatures, heating is not required.

The above-mentioned means of (c) for recovering $[^{15}O]CO$ can also be connected to another gas flow pass. For example, it can be directly connected to an inhalation apparatus for
5 enabling a PET subject to inhale a tracer gas. The connection of the means of (c) to an inhalation apparatus is preferable since it enables tracer gases with short half-lives to be rapidly supplied to a subject. Alternatively, the means of (c) can also be connected to a line for producing carbon dioxide,
10 as described later. In the case of connection to a line for the production of carbon dioxide, the gas to be irradiated need not pass through a soda lime column.

Next, the present invention relates to methods of producing $[^{15}O]CO_2$, which comprise the steps of:
15   (1) contacting $[^{15}O]CO$ with an oxidizing catalyst in the presence of dry oxygen; and

    (2) recovering the $[^{15}O]CO_2$ which is produced.

In the $[^{15}O]CO_2$ production methods of the present invention, an "oxidizing catalyst" means a catalyst capable of oxidizing
20 carbon monoxide in the presence of oxygen to produce carbon dioxide. An oxidizing catalyst in the present invention preferably expresses catalytic action without heating. The phrase "catalytic action without heating" refers to sufficient catalytic action even at room temperature, without involving a
25 positive heating operation. Oxidizing catalysts that develop catalytic action under heated conditions can still be utilized as oxidizing catalysts in the present invention, so long as they comprise the necessary catalytic ability under non-heated conditions.

30   Specifically, oxidizing catalysts in the present invention comprise a manganese dioxide-copper oxide (II) catalyst. A reaction in which the manganese dioxide-copper oxide (II) catalyst oxidizes carbon monoxide in the presence of oxygen to produce carbon dioxide is well known. However, this kind of
35 catalyst has not been found useful for producing the $[^{15}O]CO_2$ necessary for PET examination of cerebral oxygen metabolism.

In the present invention, commercially available manganese dioxide-copper oxide (II) catalysts can be used as they are. For example, a 150 mm long glass tube of ϕ 12 mm outer diameter is filled with 2 g of a manganese dioxide-copper oxide (II)

5 catalyst and dried by heating at 120°C for two hours. After cooling, the manganese dioxide-copper oxide (II) catalyst is contacted with carbon monoxide gas in the presence of dry oxygen. The manganese dioxide-copper oxide (II) catalysts that can be utilized in the present invention comprise, for example,

10 CARULITE® Catalyst (manufactured by STREM Chemicals, INC (Newburyport, MA, USA)). As described above, the concentration of carbon monoxide gas is 0.5% or less, and oxygen is supplied in an amount necessary for an oxidation reaction.

Carbon dioxide can also be added to oxygen as a carrier

15 for $C^{15}O_2$. Non-radioactive carbon dioxide added to dry oxygen acts as a carrier for $C^{15}O_2$ produced by oxidizing catalysts, and contributes to enhancement of the radiochemical purity of $C^{15}O_2$ in the final product. The amount of carbon dioxide added as a carrier may be suitably selected depending on the mixing ratio

20 of oxygen to carbon dioxide, and the flow rate of the mixed gas. For example, the above-mentioned non-radioactive carbon dioxide can be added to the mixed gas so as to be 2.5 v/v% or less of the $[^{15}O]CO_2$ produced as described above. Specifically, suitable oxidation conditions can be obtained by supplying 10

25 mL/min of oxygen gas for 300 mL/min of the gas to be irradiated. When carbon dioxide is added as a carrier, oxygen gas comprising 50 v/v% carbon dioxide may be supplied at 10 mL/min.

In addition to the manganese dioxide-copper oxide (II) catalyst, a palladium/silica gel and a catalyst of manganese

30 dioxide-copper oxide (II) to which cobalt oxide and silver oxide are added can also be utilized as oxidizing catalysts in the present invention. These catalysts are commercially available, or can also be produced based on known methods.

In the production of $[^{15}O]CO_2$ of the present invention, the

35 methods for producing $[^{15}O]CO$ are not limited. The objective of the present invention is to provide methods for $[^{15}O]CO_2$

production that do not require a heating process. Therefore, ideally, $[^{15}O]CO$ to be utilized as a raw material can also be produced by methods that do not require a heating process. Accordingly, the above-mentioned $[^{15}O]CO$ production methods are

5 preferable as methods for supplying raw material for the $[^{15}O]CO_2$ production methods of the present invention.

In the $[^{15}O]CO_2$ production methods of the present invention, $[^{15}O]CO$ is contacted with oxidizing catalysts in the presence of dry oxygen. In the present invention, a mixed gas of dry

10 oxygen and dry carbon dioxide can also be utilized as dry oxygen.

"Dry oxygen" and "dry carbon dioxide" respectively mean oxygen and carbon dioxide from which water is removed. These dry gases can be obtained by contacting an oxygen gas or carbon

15 dioxide gas with a desiccant such as a silica gel column. Silica gel used as a desiccant is typically dried at 120°C for three hours. Dry oxygen and dry carbon dioxide for use in the present invention can be obtained by using any dessicant, as long as that dessicant has a lower water content than that of a

20 dry gas obtainable using a silica gel column. More specifically, oxygen or carbon dioxide gases with a water content of 2 ppm or less can be used as a dry gas.

Dry oxygen can be used in an amount capable of sufficiently oxidizing $[^{15}O]CO$ in the presence of an oxidizing

25 catalyst to be used. Therefore, the amount of oxygen added is regulated depending on the nature of the $[^{15}O]CO$ used as a raw material, and of the oxidizing catalyst. Those skilled in the art can easily set suitable conditions.

When, for example, the above-mentioned manganese dioxide-

30 copper oxide (II) catalyst is used as a catalyst, a side reaction due to heat generation may occur if the concentration of carbon monoxide is high. Therefore, the condition of carbon monoxide concentration may be, for example, 0.5% v/v or less, specifically in the range of 0.05% to 0.3% v/v, preferably

35 0.07% to 0.2% v/v. The dry oxygen concentration in this case is, for example, 5% v/v or less, typically from 1 to 5% v/v,

preferably from 2 to 4% v/v.

When a manganese dioxide-copper oxide (II) catalyst is used as the oxidizing catalyst, the temperature at which the catalyst is used is not particularly limited. A manganese
5 dioxide-copper oxide (II) catalyst can usually catalyze the oxidation reaction of carbon monoxide at 10-40°C. The reaction can be conducted at any temperature within this temperature range. Therefore, the reaction may be carried out without positive temperature control, or by heating oxidizing catalysts
10 in a range that does not impede the time reduction.

$[^{15}O]CO_2$ produced by the action of oxidizing catalysts is recovered and purified, as necessary, and can then be utilized as an inhalation gas for PET examination of cerebral oxygen metabolism. According to the methods for producing $[^{15}O]CO_2$ of
15 the present invention, $[^{15}O]CO_2$ can be obtained by the oxidation of $[^{15}O]CO$ as a raw material. Therefore, removal of $[^{15}O]CO$ is not necessary in the present invention. Since removal of $[^{15}O]CO$ is not required, a heating process is not required either. Consequently, if $[^{15}O]CO$ is supplied as a raw material
20 by a method that does not require a heating process, production methods that do not require heating for any process can be realized.

The $[^{15}O]CO_2$ production methods based on the present invention can be performed using, for example, the above-
25 described $[^{15}O]CO$ production apparatus of the present invention. Specifically, a flow pass is set up that branches from the means for recovering the $[^{15}O]CO$ supplied by the above-mentioned $[^{15}O]CO$ production apparatus, and mixes dry oxygen gas, or a gas mixture of dry oxygen and dry carbon dioxide gas, and guides
30 the resultant mixture to the oxidizing catalysts. The organization of such a flow pass is shown in Fig. 1. Solenoid valves can be placed before and after an oxidizing catalyst to control the amount of raw material gas supplied to the oxidizing catalysts, and the flow rate of the resulting ^{15}O-
35 carbon dioxide. Furthermore, a silica gel column for drying oxygen can also be provided in an oxygen-supplying pass.

Similar to above-mentioned $[^{15}O]CO$, $[^{15}O]CO_2$ produced by the present invention can be supplied directly to an inhalation apparatus, as an inhalation gas for PET examination of cerebral oxygen metabolism.

5   All prior art literature cited in the present specification is incorporated herein by reference.

Brief Description of the Drawings

Fig. 1 is a diagram showing the organization of an
10   apparatus for supplying $[^{15}O]CO$ and $[^{15}O]CO_2$ according to the present invention.

Fig. 2 is a diagram showing the organization of a system according to the present invention for producing $[^{15}O]CO$ and $[^{15}O]CO_2$, and for measuring their radiochemical purity.

15

Best Mode for Carrying out the Invention

Herein below, the present invention is specifically illustrated using Examples, but is not to be construed as being limited thereto.

20

[EXAMPLE 1]

A system for producing $[^{15}O]CO$ and measuring radiochemical purity is shown in Fig. 2. As the gas to be irradiated, a high-purity nitrogen gas (99.9999 or more) comprising 0.1%
25   carbon monoxide was flowed continuously into a target box at a flow rate of 300 mL/min. The target box was continuously irradiated with deuterons to cause the nuclear reaction of $^{14}N(d,n)^{15}O$. The out-flowing reaction product was purified without heating, by passing through a column filled with
30   activated carbon and soda lime. The $[^{15}O]CO$ comprised in the gas to be irradiated after purification was analyzed by radio-chromatography to reveal radiochemical purity of 99% or more .

[EXAMPLE 2]

35   The gas to be irradiated comprising $[^{15}O]CO$, obtained under the same conditions as in Example 1, was passed through a

column filled with silica gel and activated carbon. Subsequently, dry oxygen (10 mL/min) dried with silica gel and a gas mixture (10 mL/min) of dry oxygen with 50 v/v% of dry carbon dioxide were added to the gas to be irradiated. Further,

5   the mixture was passed through a manganese dioxide-copper oxide (II) catalyst. As the manganese dioxide-copper oxide (II) catalyst, CARULITE® Catalyst (manufactured by STREM Chemicals, INC (Newburyport, MA, USA)) was used.

   $[^{15}O]CO_2$ comprised in the gas to be irradiated after

10   oxidation by a catalyst was analyzed by radio-chromatography to reveal radiochemical purity of 96% or more. In particular, when a gas mixture (10 mL/min) comprising 50 v/v% of dry carbon dioxide was used, radiochemical purity increased to 99 v/v% or more.

15

Industrial Applicability

   The present invention provides methods for synthesizing $[^{15}O]CO$ or $[^{15}O]CO_2$ that do not require a heating process. ^{15}O gas could already be synthesized without a heating process.

20   Therefore, the present invention makes it possible to supply all three of the gases necessary for a cerebral oxygen metabolism examination based on PET, without a heating process.

   PET examination of cerebral oxygen metabolism provides important information for determining initial therapeutic

25   strategies for cerebral stroke attacks. However, examination based on known methods takes two hours. The heating process in the synthesis of tracer gases occupies most of the examination time, becoming a significant cause of impeded reduction of examination time. The present invention realizes a substantial

30   reduction in examination time, since synthesis of all tracer gases can be performed without heating process.

   For example, $[^{15}O]CO$ gas is synthesized using the apparatus for synthesizing a tracer gas as described in the Examples. The gas to be irradiated, necessary for production of the

35   $[^{15}O]CO$ gas, can be completely prepared in one minute. Since the present invention does not require a heating process,

tracer gas synthesis can be immediately initiated if a cyclotron for deuteron irradiation is prepared. In contrast, known methods cannot synthesize tracer gases until heating is complete. The heating process requires around 30 minutes.

5   The following example (Table 1) shows the time required for a method of the present invention (low-temperature rapid synthesis method) compared with conventional methods, which require 26 minutes for heating. The method of the present invention saves 25 (26-1) minutes. That is, according to the

10   present invention, the time required to examine cerebral oxygen metabolism, which is known to be about two hours, can be reduced by 20% or more.

Table 1

Major preparation steps	Required times (min)			
	0	10	20	30
<u>Low-temperature rapid synthesis method</u>				
Cyclotron start-up	⟶ 8 min			
[¹⁵O]CO synthesis preparation	⟶1 min			
<u>Conventional method</u>*				
Cyclotron start-up	⟶8 min			
[¹⁵O]CO synthesis preparation	Temperature rising ⟶26 min			

CLAIMS

1.   A method for producing ^{15}O-carbon monoxide, which comprises
the steps of:

5   (1) using a nitrogen gas comprising carbon monoxide as a
gas to be irradiated, and irradiating the gas with a deuteron
beam; and

        (2) recovering ^{15}O-carbon monoxide produced by the deuteron
beam irradiation.

10

2.   The method according to Claim 1, wherein the amount of
carbon monoxide comprised in the gas to be irradiated is 0.01
to 0.5 v/v%.

15   3.   The method according to Claim 2, wherein the amount of
carbon monoxide comprised in the gas to be irradiated is 0.05
to 0.2 v/v%.

4.   The method according to Claim 1, which comprises the step
20   of contacting the irradiated gas with a nitrogen oxide
adsorbent and/or a carbon dioxide adsorbent, and recovering ^{15}O-
carbon monoxide.

5.   The method according to Claim 1, wherein the gas to be
25   irradiated is continuously supplied while recovering the
produced ^{15}O-carbon monoxide.

6.   An apparatus for producing ^{15}O-carbon monoxide, which
comprises:

30   (1) a target box through which a gas to be irradiated can
be passed and in which the gas to be irradiated can be
irradiated with a deuteron beam;

        (2) a means of supplying the gas to be irradiated, which
supplies the target box of (1) with a nitrogen gas comprising
35   carbon monoxide as the gas to be irradiated; and

        (3) a means for recovering ^{15}O-carbon monoxide.

7. The apparatus according to Claim 6, wherein the means of (3) for recovering ^{15}O-carbon monoxide comprises:

a means for receiving the gas to be irradiated in the target box of (1); and

a nitrogen oxide adsorbent and/or a carbon dioxide adsorbent.

8. The apparatus according to Claim 6, wherein the means for supplying the gas to be irradiated of (2) can continuously supply the target box of (1) with the gas to be irradiated.

9. The apparatus according to Claim 6, wherein the means of (3) for recovering ^{15}O-carbon monoxide is connected to a line for supplying ^{15}O-carbon monoxide to a subject.

10. A method for producing ^{15}O-carbon dioxide, which comprises the steps of:

(1) contacting ^{15}O-carbon monoxide with an oxidizing catalyst in the presence of dry oxygen; and

(2) recovering the produced ^{15}O-carbon dioxide.

11. The method according to Claim 10, wherein the dry oxygen is a mixed gas comprising dry carbon dioxide.

12. The method according to Claim 10 for producing ^{15}O-carbon monoxide, which comprises the steps of:

i) supplying the target box with a nitrogen gas comprising carbon monoxide as the gas to be irradiated; and

ii) irradiating the gas to be irradiated with a deuteron beam to produce ^{15}O-carbon monoxide.

13. An apparatus for producing ^{15}O-carbon dioxide, which comprises:

(1) a means for supplying ^{15}O-carbon monoxide;

(2) an oxidizing catalyst for oxidizing carbon monoxide;

(3) a means for supplying dry oxygen to the oxidizing catalyst; and

(4) a means for recovering ^{15}O-carbon dioxide.

5   14. The apparatus according to Claim 13, wherein the means of (1) for supplying ^{15}O-carbon monoxide is a ^{15}O-carbon monoxide-producing apparatus that comprises:

i) a target box through which a gas to be irradiated can be passed, and in which the gas to be irradiated can be

10   irradiated with a deuteron beam; and

ii) a means for supplying the gas to be irradiated which supplies the target box of (i) with a nitrogen gas comprising carbon monoxide as the gas to be irradiated.

15   15. A method for producing ^{15}O-carbon monoxide and ^{15}O-carbon dioxide, which comprises the steps of:

(1) using a nitrogen gas comprising carbon monoxide as a gas to be irradiated, and irradiating the gas with a deuteron beam;

20   (2) recovering the ^{15}O-carbon monoxide produced by the deuteron beam irradiation;

(3) contacting the irradiated gas with an oxidizing catalyst in the presence of dry oxygen; and

(4) recovering ^{15}O-carbon dioxide produced in the step of

25   (3).

16. An apparatus for producing ^{15}O-carbon monoxide and ^{15}O-carbon dioxide, which comprises:

(1) a target box through which a gas to be irradiated can

30   be passed, and in which the gas to be irradiated can be irradiated with a deuteron beam;

(2) a means for supplying the gas to be irradiated, which supplies the target box with a nitrogen gas comprising carbon monoxide as the gas to be irradiated;

35   (3) a means for recovering ^{15}O-carbon monoxide;

(4) an oxidizing catalyst for oxidizing carbon monoxide;

(5) a means for supplying dry oxygen to the oxidizing catalyst; and
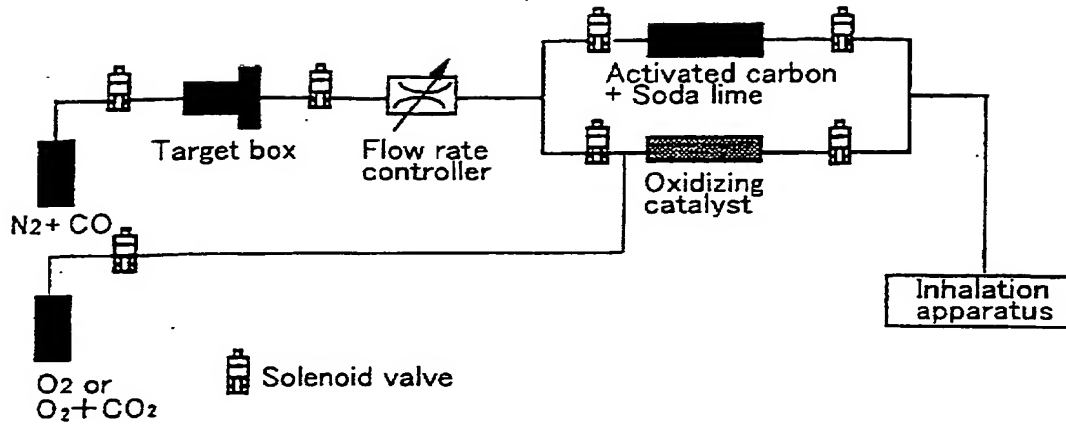
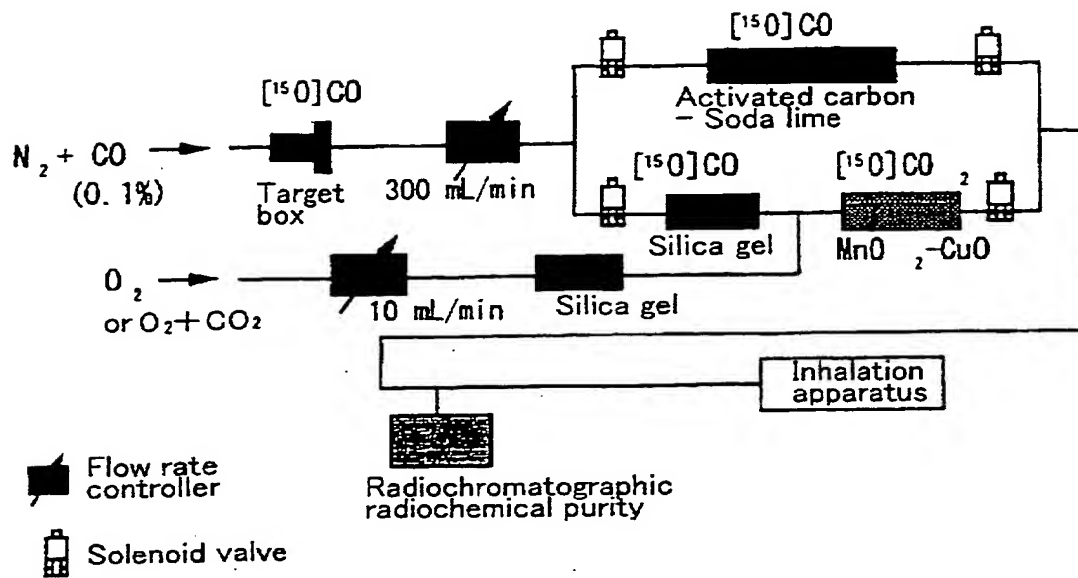(6) a means for recovering ^{15}O-carbon dioxide.

FIG. 1

FIG. 2